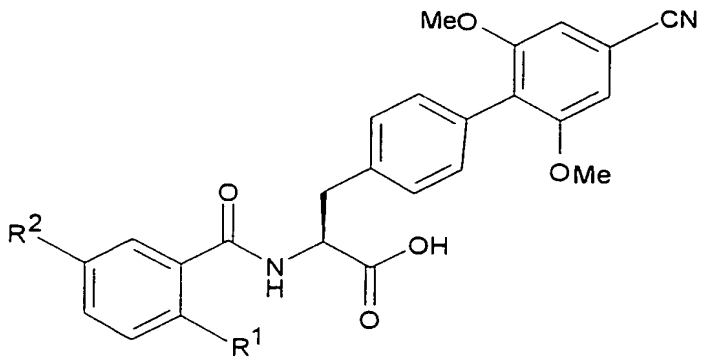
DISCLOSURE OF INVENTION

The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

in which

R^1 is bromo; and

R^2 is halogen, C_{1-6}alkyl or C_{1-6}alkoxy.

Preferably R^2 is halogen or C_{1-6}alkoxy.

More preferably R^2 is fluoro, methoxy or ethoxy.

In a further aspect, the present invention provides E1-E7 (as described below) or a pharmaceutically acceptable derivative thereof, i.e.

(S)-2-{[1-(2-Bromo-5-ethoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-fluorophenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[1-(2-Bromo-5-methylphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid;

(*S*)-2-{[(2-Bromo-5-chlorophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid;

(*S*)-2-{[(2,5-Dibromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid;

(*S*)-2-{[(5-(*iso*-Propoxy)-2-bromophenyl)methanoyl]amino}-3-[4'-cyano-2',6'-dimethoxybiphenyl-4-yl]propionic acid
or a pharmaceutically acceptable derivative thereof.

Throughout the present specification, unless otherwise stated:
the term "halogen" is used to describe a group selected from fluorine, chlorine, bromine or iodine;
the term " C_{1-6}alkyl" is used to describe a group or a part of the group comprising a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl;
the term " C_{1-6}alkoxy" is used to describe a group or a part of the group wherein an oxygen atom is bound to the above mentioned C_{1-6}alkyl group; examples of such groups include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, tert butoxy, pentoxy or hexoxy.

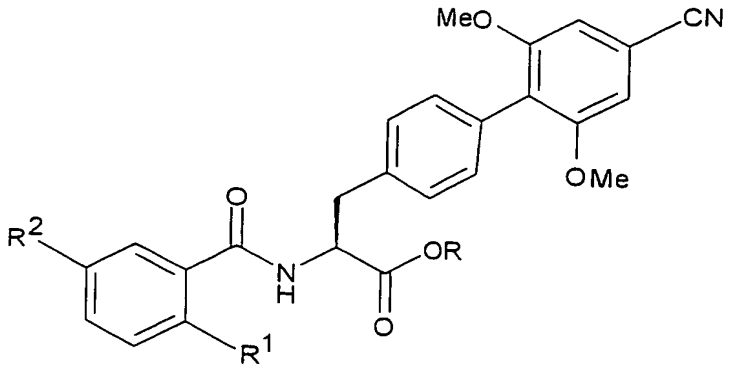
The characteristics of the present compounds are the introduction of a cyano group at the 4'-position of the biphenyl nucleus in combination with the claimed 2,5- di-substituted benzoyl group.

The compounds of the formula (I) or a pharmaceutically acceptable derivative thereof have potent inhibitory activity against α_4 integrin mediated cell adhesion. Further, it has been found that certain Examples show excellent bioavailability after oral administration and / or good systemic exposure.

E1, E2 and E3 (as described below) exhibit an advantageous combination of the above characteristics.

It will be appreciated that the compounds of formula (I) or a pharmaceutically acceptable derivative thereof may have more than one asymmetric carbon atoms and therefore may occur as diastereomers. All such isomeric forms are included within the present invention, including mixtures thereof.

Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or HPLC. A single stereoisomeric form of the compound may also be prepared from a corresponding optically pure intermediate or

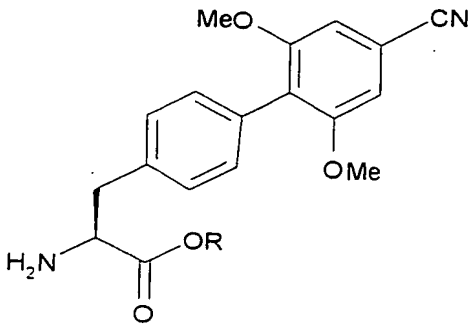


(II)

in which R^1 and R^2 are as defined in formula (I) and R is a group capable of forming a carboxylic acid ester and optionally thereafter forming a pharmaceutically acceptable derivative thereof.

An example of a suitable R group is C_{1-6}alkyl such as methyl or t-butyl, preferably methyl. Hydrolysis may either occur via an acidic or an alkaline medium. An illustration of hydrolysis in an alkaline medium would be treating the compound of formula (II) with an alkali metal hydroxide in a suitable solvent e.g. treatment with lithium hydroxide in aqueous tetrahydrofuran. An illustration of hydrolysis in an acidic medium would be treating the compound of formula (II) with a mineral acid in a suitable co-solvent at elevated temperature e.g. treatment with 5N hydrochloric acid in dioxane at 60°C overnight. Such methods are familiar to those skilled in the art.

The compounds of formula (II) can be prepared by reacting a compound of formula (III) or an acid addition salt thereof:



(III)

Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The carrier or diluent must be acceptable in the sense of being not deleterious to the recipient thereof. The pharmaceutically acceptable carrier or diluent may be, for example, binders (e.g., syrup, gum arabic, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone), excipients (e.g., lactose, sucrose, corn starch, potassium phosphate, sorbitol, glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol, silica), disintegrators (e.g., potato starch), wetting agents (e.g., sodium laurylsulfate), and the like.

The routes for administration (delivery) of the composition of the invention include, but are not limited to, one or more of: oral (e. g. as a tablet, capsule, or as an ingestible solution), topical, mucosal (e. g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e. g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, epidural, sublingual.

For example, the compound can be administered orally in the form of tablets, capsules, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included. Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

A proposed dose of the compounds according to the present invention for administration to a human (of approximately 70kg body weight) is 0.1mg to 2g, more typically 0.1mg to 1g, of the active ingredient per unit dose, expressed as the weight of free acid. The unit dose may be administered, for example, 1 to 4 times per day. The dose will depend on the route of administration. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient as well as the severity of the condition. The dosage will also depend on the route of administration. The precise dose and route of administration will ultimately be at the discretion of the attendant physician or veterinarian.

The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art. It will be appreciated that the amount of a compound of the invention required for use in treatment or prevention will vary with the nature of the condition and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. Examples of other active agents that may be combined with the compound of formula (I) or a pharmaceutically acceptable derivative thereof include, but not limited to: (a) other VLA-4 antagonists; (b) H1 histamine antagonists; (c) NSAID's; (d) anti-diabetic agent e.g. glitazones (e) anti-cholinergic agents (f) COX-2 inhibitors e.g. 2-(4-ethoxy-phenyl)-3-(4-methanesulfonyl-phenyl)-pyrazolo[1,5-b]pyridazine (as disclosed in patent application WO 99/12930); (g) PDE-IV inhibitors; (h) steroids e.g. corticosteroids; (i) beta agonists; (j) antagonists of the chemokine receptors e.g. CCR-2, CCR-3, CCR-5 and CCR-8; (k) suitable multiple sclerosis treatments or preventions such as interferon; (l) LFA-1 antagonists; (m) TNF inhibitors; (n) Sulphasalazine and 5-aminosalicylates and (o) Immunosuppressants.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a

dihloromethane and a drop of dimethylformamide}. The reaction was stirred at 0°C for 1 hour and was then diluted with a saturated aqueous solution of sodium hydrogen carbonate (200 mL). After separation of the organic layer, the aqueous layer was re-extracted with dichloromethane (2 x 400 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated at reduced pressure. The product was purified by silica gel chromatography (Biotage 75L, 800 g silica) eluting with ethyl acetate: dichloromethane (3:97) to yield the title compound as a colourless solid; MS (ES+ve): $[M+H]^+$ at m/z 567, 569 ($C_{28}H_{27}BrN_2O_6$ requires $[M+H]^+$ at m/z 567, 569).

Preparation 12

(S)-2-{[1-(2-Bromo-5-methoxyphenyl)methanoyl]amino}-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester (P12)

2-Bromo-5-methoxybenzoic acid (0.355 g, 1.54 mmol, Aldrich), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.168 g, 2 equiv.), and triethylamine (1.069 mL, 5 equiv.) were added to dimethylformamide (25 mL) under argon with stirring at room temperature. After 0.5 hour the ethyl ester corresponding to P7 (P13), (S)-2-amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester hydrochloride, (0.6 g, 1 equiv.) was added and stirring continued overnight. The solvent was then evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was washed with water (x 2) and saturated aqueous sodium bicarbonate before evaporation to dryness. The crude product was purified by column chromatography on silica with a gradient of 0-10% methanol in dichloromethane and subsequently by preparative HPLC to give the title compound.

MS (AP+ve): $[M+H]^+$ at m/z 567, 569 ($C_{28}H_{27}BrN_2O_6$ requires $[M+H]^+$ at m/z 567, 569).

Preparation 13

(S)-2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid ethyl ester hydrochloride (P7 - corresponding ethyl ester) (P13)

Thionyl chloride (7.71 mL, 105.7 mmol) was added dropwise over 15 minutes to a solution of (S)-2-tert-butoxycarbonylamino-3-[4'-(hydroxyiminomethyl)-2',6'-dimethoxybiphenyl-4-yl]propionic acid ethyl ester (12.5 g, 26.5 mmol) [prepared analogously to the sequence P1-P6 except commencing in Preparation 1 with L-tyrosine ethyl ester hydrochloride (from Bachem) instead of L-tyrosine methyl ester hydrochloride] in dichloromethane (250 mL) at 0°C under argon. The reaction stirred for a further 15 minutes at batch temperature and then allowed to warm to room temperature and

was filtered, washed with water and dried at 40°C under vacuum to yield the title compound as an off-white solid.

^{1}H NMR δ (DMSO-d_6): 3.78 (6H, s), 7.0 (2H, s), 9.25 (2H, s)

(S)-2-Amino-3-(4'-cyano-2',6'-dimethoxybiphenyl-4-yl)propionic acid methyl ester hydrochloride

A solution of di-*tert*-butyldicarbonate (17.9 g, 81.8 mmol) in toluene (60 mL) was added dropwise to a solution of (S)-methyl tyrosine (from Flamma, 15.2 g, 77.9 mmol) in toluene (120 mL) at 90°C. The reaction mixture was stirred at 90°C for at least 30 minutes. Once complete by HPLC, the reaction mixture was cooled to 0°C and pyridine (19 mL, 0.23 mol) added keeping the temperature at 0°C. Trifluoromethanesulfonic anhydride (16.7 mL) was added dropwise keeping the temperature at 0°C. The orange slurry was stirred at 0°C for at least 2 hours. Once complete by HPLC 2M hydrochloric acid (133 mL) was added keeping the temperature at 0°C. The layers were separated and the upper organic layer washed with 10%w/w aqueous sodium carbonate solution (138 mL) and 36%w/w brine (138 mL). The organic layer was concentrated to approximately 60 mL and solid sodium chloride (30 g) added, followed by n-heptane (300 mL). The mixture was filtered and the filtrate extracted into 1-methyl-2-pyrrolidone (2x150 mL). Residual volatile organic solvents were distilled under vacuum. 4-Cyano-2,6-dimethoxyphenylboronic acid (17.5 g, 84.5 mmol) was added and the solution degassed. Tetrakis(triphenylphosphine) palladium(0) (3g, 2.7 mmol) and triethylamine (19.8 mL) were added and the reaction mixture heated to 70°C. The reaction was stirred at 70°C for at least 2 hours. Once complete by HPLC, the reaction mixture was transferred into another vessel and diluted with toluene (300 mL). 2M Hydrochloric acid (300 mL) was added and the mixture filtered. The organic layer was separated and washed with water (300 mL). The organic layer was filtered and washed through with toluene (90 mL). The toluene solution was stirred with Silicycle silica supported N-functionalised thiourea (11.7 g) for at least 15 hours. The silica was filtered and washed with toluene (30 mL). The solution was dried azeotropically then slowly added to a solution of hydrogen chloride in isopropanol (155 mL at 5M concentration) at 50°C. The reaction mixture was stirred at 50°C for 30 minutes until complete by HPLC. The mixture was cooled to 20°C and the product filtered off under vacuum and washed with toluene (60 mL). The solid was dried *in vacuo* at 40°C to yield the title compound as an off-white solid.

2-Bromo-5-hydroxybenzoic acid methyl ester